Tetrahedron Letters 55 (2014) 264–266

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalytic aromatization of 1,4-dihydropyridines by radical cation salt prompted aerobic oxidation

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ARTICLE INFO

Article history:
Received 16 September 2013
Revised 28 October 2013
Accepted 5 November 2013
Available online 13 November 2013

Keywords:
1,4-Dihydropyridines
Aromatization
Radical cation
Catalytic oxidation

ABSTRACT

Aromatization of Hantzch 1,4-dihydropyridines was achieved under radical cation salt induced conditions, in which triarylamine radical cation acts as an efficient catalyst to prompt the aerobic oxidation of 1,4-DHPs in a catalytic way.

Hantzsch 1,4-dihydropyridines (1,4-DHPs) as a class of excellent antioxidants have received extensive research. Besides their broad applications in the treatment of cardiovascular diseases such as hypertension and angina pectoris,[1] oxidative aromatization of DHPs, which was used to model the biological hydride transfer mechanism of coenzyme NADH, has attracted continuing interests of organic and medicinal chemists and massive amount of protocols has been developed.[2–6] A variety of catalyst systems have been founded for the aromatization of DHPs. In early works, stoichiometric or excess amount of strong oxidants were mostly used, such as $Zr(NO_3)_4$, CAN, CrO_2, HNO_3, MnO_2, $NaIO_4$, and $Mn(OAc)_3$.[2] Recently, more attention has been paid to catalytic aromatization of DHPs using molecular oxygen as a clean source of oxidant. Since oxygen itself does not oxidize 1,4-DHP effectively, an appropriate catalyst prompted condition is necessary. For this purpose, aerobic oxidation using $RuCl_3$, Pd/C, activated carbon, and $Fe(ClO_4)_3$ in acetic acid has thus been developed.[3] Additionally, Tung reported a photocatalytic aromatization of 1,4-DHP by platinum(II) terpyridyl complexes with the release of H_2.[4] Liu and co-workers also reveal an aerobic aromatization catalyzed by N-hydroxyphthalimide (NHPI).[5] More recently, Liu and Li et al. established a mild aerobic oxidation of 1,4-DHPs using 9-phenyl-10-methylacridinium as a reusable organocatalyst.[6] Although these elegant methods have been established, some limitations still confine their further applications, such as low catalytic efficiency, inconvenient preparation of catalyst, limited scope, and harsh reaction condition. Therefore, the development of more convenient, efficient, and general catalytic oxidation remains a challenging task in this hot area.

Recently, we reported, for the first time, the catalytic radical cation initiated C–H functionalization of glycine derivatives with styrenes to forge quinoline skeletons in both inter- and intramolecularly ways (Fig. 1A).[7] This method represented a catalytic approach to sp^3 C–H bond oxidation, avoiding use of excess quantities of the oxidants. In this reaction, tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\cdot}$) is the crucial catalyst to activate molecular oxygen participating in aerobic oxidation of sp^3 C–H bond. Inspired by this work, we questioned whether this catalytic system could also be applied to the aromatization of 1,4-DHPs (Fig. 1B). Herein, we wish to report a new method for the catalytic aromatization of 1,4-DHPs using radical cation salt as a catalyst.

At the outset, the aromatization of **1a** was chosen as the model reaction to screen the best reaction conditions (Table 1). In the presence of 1 mol % of $TBPA^{+\cdot}$ under air atmosphere, the desired aromatization product **2a** was isolated in 25% yield (entry 1). Higher catalyst loading increased the yields, and when 5 mol % of the catalyst added, the pyridine product was obtained in nearly quantitative yield (entry 3). If $TBPA^{+\cdot}$ was increased to 10 or 15 mol %, the reaction become faster, but the yield decreased about 10%, probably due to over oxidation. We also performed the model reaction in oxygen atmosphere, and lower isolated yield was obtained, probably due to further oxidation. Next, solvent screen was conducted (entries 7–10). The results show that acetonitrile was the best solvent, and other nonpolar solvent gave lower yields of the desired product. In the absence of $TBPA^{+\cdot}$ and oxygen

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.11.010

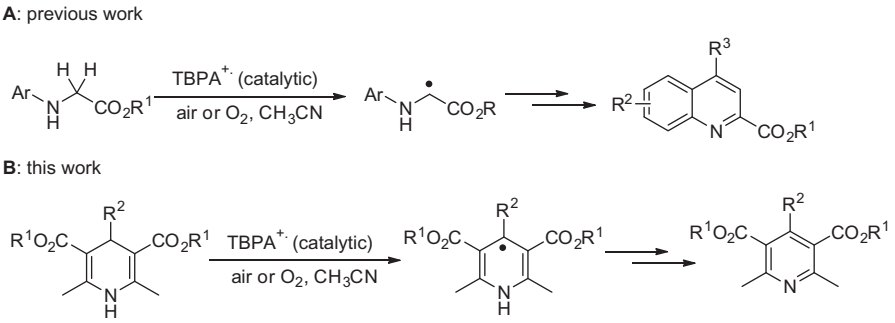
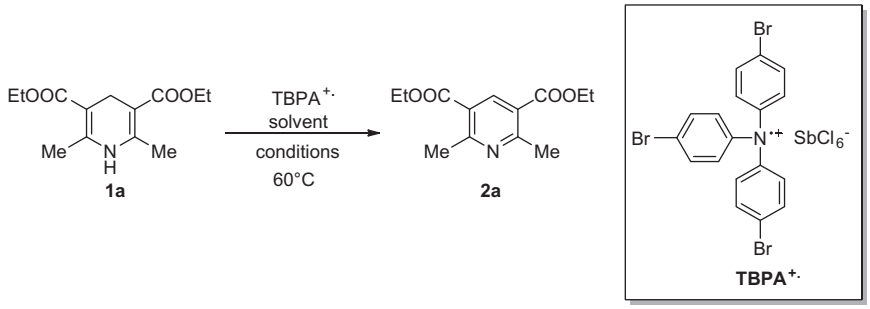


Figure 1. Catalytic aromatization of 1,4-DHPs.

Table 1
Optimization of the reaction conditions



Entry	TBPA$^{+\cdot}$ (mol %)	Solvent	Condition	Time (h)	Yield[a] (%)
1	1	CH_3CN	Air	64	25
2	3	CH_3CN	Air	48	82
3	5	CH_3CN	Air	6	98
4	10	CH_3CN	Air	5	88
5	15	CH_3CN	Air	3	73
6	5	CH_3CN	O_2	6	82
7	5	THF	Air	8	86
8	5	$ClCH_2CH_2Cl$	Air	4	62
9	5	$CHCl_3$	Air	9	77
10	5	CH_2Cl_2	Air	9	70
11	0	CH_3CN	Air	48	0
12	5	CH_3CN	Ar	48	Trace

[a] Isolated yield based on **1a**.

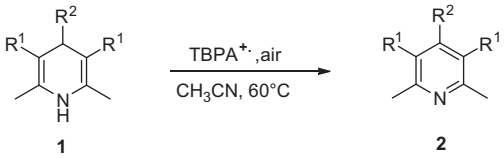
respectively, no reaction occurred which implied that both TBPA$^{+\cdot}$ and oxygen are crucial to achieve the aromatization of 1,4-DHPs.

With the optimized conditions in hand, we employed various 1,4-DHPs to test the generality of this reaction and the results are compiled in Table 2. In all the cases, the expected products **2** were obtained in good yields. 4-Alkyl-1,4-DHPs were more reactive than 4-aryl-1,4-DHPs, and their aromatization was achieved in a shorter reaction time (entries 1–4). Among 4-aryl-1,4-DHPs, electron-donating groups exert positive effect on the reaction, and higher yields were obtained (entries 5–10). Even relatively inert nitrophenyl-substituted 1,4-DHPs, whose aromatization failed by reported method, show good reactivity in the standard reaction conditions, affording the desired products in good yields (entries 9 and 10).[5] When 4-benzyl substituted 1,4-DHP was used, the corresponding dealkylated product **2a** was isolated in 78% yield (entry 11). The aromatization of 4-alkenyl-1,4-DHP occurred smoothly, which exhibited good functional group tolerance and allowed further functionalization of the pyridine derivatives (entry 12). Then, the reactivity of heterocycle Hantzsch 1,4-DHPs were tested (entries 13 and 14). In the case of 4-furyl-1,4-DHP, 42% of C–C cleavaged product **2a** was formed along with the normal aromatization product **2m**.[6] 2-Pyridyl-1,4-DHP can also be tolerated in the standard conditions, albeit higher catalyst loading is needed, and the desired bipyridine product was isolated in 63% yield (entry 14). 4-Ester substituted 1,4-DHP was also a good candidate of the aromatization, giving the pyridine product in 69% yield (entry 15). Other 1,3-dicarbonyl derivated 1,4-DHPs were then employed to broaden the scope of application. Again the aromatization proceeded efficiently under the TBPA$^{+\cdot}$ catalyzed aerobic oxidation (entries 16 and 17).

Based on the result obtained and literature reports,[5,7] a possible mechanism was proposed for the catalytic aerobic oxidation (Scheme 1). A peroxy radical cation A was generated by coupling of TBPA and oxygen, which abstracts a hydrogen atom from 1,4-DHP. The corresponding free radical intermediate was further oxidized by oxygen or peroxide intermediate B, producing the pyridine product. After fragmentation of the intermediate B, TBPA$^{+\cdot}$ is regenerated to prompt the further oxidation reaction.

In summary, we demonstrated an efficient aromatization of 1,4-DHPs. Aerobic oxidation prompted by catalytic amounts of triarylaminium radical cation salt was achieved under mild conditions, avoiding harsh reaction conditions, and addition of excess

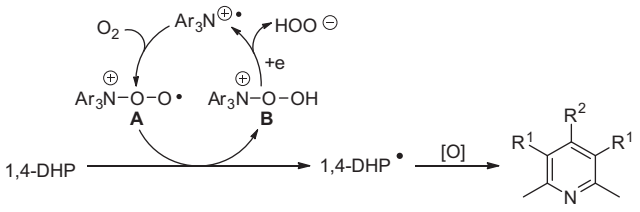
Table 2
Scope of radical cation mediated catalytic aromatization[a]



1 2

Entry	1	R^1	R^2	Time	2	Yield[b] (%)
1	**1a**	CO_2Et	H	6	**2a**	98
2	**1b**	CO_2Et	Me	6	**2b**	89
3	**1c**	CO_2Et	Et	6	**2c**	84
4	**1d**	CO_2Et	*n*-Pr	6	**2d**	73
5	**1e**	CO_2Et	*p*-$MeOC_6H_4$	10	**2e**	88
6	**1f**	CO_2Et	Ph	18	**2f**	78
7	**1g**	CO_2Et	*o*-ClC_6H_4	22	**2g**	69[c]
8	**1h**	CO_2Et	*p*-FC_6H_4	32	**2h**	66
9	**1i**	CO_2Et	*p*-$NO_2C_6H_4$	48	**2i**	63[d]
10	**1j**	CO_2Et	*m*-$NO_2C_6H_4$	20	**2j**	74[d]
11	**1k**	CO_2Et	Bz	18	**2a**	78
12	**1l**	CO_2Et	Styryl	14	**2l**	70
13	**1m**	CO_2Et	2-Furyl	30	**2m**, **2a**	52, 42
14	**1n**	CO_2Et	2-Pyridyl	35	**2n**	62[d]
15	**1o**	CO_2Et	CO_2Et	18	**2o**	69
16	**1p**	COMe	H	6	**2p**	78
17	**1q**	COMe	*p*-$MeOC_6H_4$	11	**2q**	64

[a] 1,4-DHP (0.5 mmol), $TBPA^{+\cdot}$ (0.025 mmol) in CH_3CN at 60 °C.
[b] Isolated yield based on **1**.
[c] $TBPA^{+\cdot}$ (0.1 mmol) was used.
[d] $TBPA^{+\cdot}$ (0.2 mmol) was used.



Scheme 1. Proposed mechanism.

oxidants. This method is superior in mild reaction conditions, good functional group tolerance, and the high efficiency of the oxidative aromatization. Further investigations and applications are still under way in this laboratory.

Acknowledgment

We thank NSFC (21002079 and 21362030) for supporting our research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.010.

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